Biography of Cornelia I. Bargmann

In the unhearing, unseeing world of the flatworm *Caenorhabditis elegans*, its sense of smell is its lifeline. Cornelia Bargmann's work has revealed many of the genetic and molecular underpinnings of *C. elegans* olfaction and has furthered the understanding of its influence on complex behaviors. Additionally, Bargmann has uncovered key signaling pathways that direct the proper wiring of the nematode's 302 neurons.

Previously at the University of California, San Francisco (UCSF), Bargmann recently moved to The Rockefeller University (New York), where she is a Howard Hughes Medical Institute investigator, Torsten N. Wiesel Professor, and head of the Laboratory of Neural Circuits and Behavior. Bargmann's research has been recognized through numerous awards, including the Lucille P. Markey Award (1990–1995) and the Searle Scholar Award (1992–1995). She was elected to the American Academy of Arts and Sciences in 2002 and the National Academy of Sciences in 2003.

In her Inaugural Article in this issue of PNAS (1), Bargmann maps out the neural circuit underlying navigation in *C. elegans*—from the neurons involved in the initial detection of food odors to the motor neurons that control the worm's movement. This article presents one of only a few behaviors that have been mapped in such a detailed way.

Cornelia I. Bargmann. Photograph courtesy of Carly Calhoun.

Academic Destiny

Growing up in Athens, GA, in a family she describes as "frighteningly well educated," Bargmann took an early liking to her science classes in junior high and high school. "I always loved science more than anything else because of the 'blue collar' aspect of it—the fact that you actually do it," she says. Bargmann's first major foray into scientific research was during her undergraduate years at the University of Georgia (Athens, GA), where her father was a professor of Computer Science and Statistics. At 17, "my first job in a science lab was the world's most menial summer job—making fly food for a population biology lab," Bargmann recalls. The laboratory head, Wyatt Anderson, took an interest in Bargmann, introducing her to Sidney Kushner in the Genetics Department. During her junior and senior years, she worked in Kushner's laboratory, studying bacterial genetics and RNA metabolism and learning molecular biology, a discipline that would provide the foundation for her later research career.

In 1981, Bargmann graduated from the University of Georgia with a degree in biochemistry and headed north to attend graduate school at the Massachusetts Institute of Technology (MIT, Cambridge, MA).

Surprising Success

As a graduate student, Bargmann studied the molecular mechanisms of oncogenesis in the laboratory of Robert Weinberg, who focused on Ras genes and their role in human tumors. Bargmann became involved in these projects and helped identify the mutation that activated Ras in human bladder cancer (2).

Bargmann's own thesis research on a non-Ras oncogene, called *neu*, turned out to have surprising clinical relevance. After cloning the *neu* oncogene from a rodent neuroblastoma and determining that it was an epidermal growth factor receptor (EGFR)-related protein (3), Bargmann then described the mutations that activated *neu* (4). Although the rodent neuroblastoma model was considered an interesting experimental model system, no human correlate was known, making its relevance to human cancer dubious. "If you had asked anyone in the Weinberg lab, 'Whose project is least likely to result in a therapy for human tumors?' everyone would have said me. Including me!" admits Bargmann.

In the years that followed, other researchers found that *neu* gene was amplified in aggressive breast tumors. The receptor, also called HER2 or erbB2, is now the target for the Herceptin (trastuzumab) antibody, which is used to treat metastatic breast cancer. Although Bargmann was not involved in developing trastuzumab, she states, "It's gratifying to have been involved in a discovery that, within your lifetime, results in a patient therapy."

Sniffing Out Olfaction

After receiving her Ph.D. from the Department of Biology in 1987, Bargmann remained at MIT for postdoctoral research in the laboratory of H. Robert Horvitz. She began to pursue a long-standing interest in the nervous system and behavior. Although she felt intimidated by the complexity of the nervous system, an exchange with David Baltimore, an MIT faculty member and Nobel laureate, jolted her into action. When Baltimore asked about her research interests, Bargmann replied that she was interested in the molecular biology of the nervous system but did not know how to approach it. "He said, 'Well, you're not very brave, are you?'"

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she recalls laughingly. "That is not something a 20-year-old needs to hear from a Nobel laureate."

Emboldened by Baltimore's provocative comment, Bargmann told Horvitz that she wanted to study chemosensory behavior in *C. elegans*, the model system used by Horvitz's laboratory. Horvitz's policy with his postdoctoral fellows was such that "we could work on anything that we wanted to, any biological problem, as long as we could address it in

This is a Biography of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 3184.

C. elegans," says Bargmann. In her readings of nematode biology, Bargmann found that, in the 1970s, researchers had shown that the worms could respond to chemical stimuli and undergo chemotaxis. However, little was known about the genetics of these behaviors, and Bargmann thus saw an opportunity to pursue her interests.

In her first study in Horvitz's laboratory, Bargmann used laser ablation to show that certain sets of chemosensory neurons in *C. elegans* were important for responding to various chemicals (5). She also identified sets of chemosensory neurons that controlled whether the worm entered into and exited from an alternative stage, called a dauer larva, that does not eat or reproduce and is highly resistant to stress (6).

Bargmann achieved another research breakthrough by elucidating the depth and breadth of the nematode's olfactory sense. She showed that *C. elegans* could detect and respond to a number of volatile chemicals, which acted as either attractants or repellents. Through laser ablation, Bargmann found that chemotaxis to volatile compounds required different sensory neurons compared with chemotaxis to water-soluble attractants, providing some of the first evidence that *C. elegans* had a sense of smell. In addition, she identified mutations in the *odr* genes that disrupted chemotaxis to some chemicals (7). At the time, *C. elegans* was known to respond to a few amino acids and salts, but Bargmann began to realize that the nematodes "had a sense of smell that detected hundreds, maybe thousands, of different odors."

A Brainy Environment

In search of a faculty position, Bargmann found that UCSF offered abundant expertise in the field she loved but lacked formal training in—neuroscience. Impressed with UCSF's rich neuroscience environment and the general enthusiasm for science of the faculty, Bargmann accepted an assistant professor position in the Department of Anatomy in 1991. Over the next 13 years, Bargmann was promoted through the ranks to full professor (1998) and served as vice chair of the department (1999–2004).

At UCSF, Bargmann continued to study how olfaction works at the molecular level. Taking advantage of newly available information about the *C. elegans* genome, Bargmann identified large families of G protein-coupled receptors (GPCRs) that appeared to be chemosensory receptors for water-soluble attractants, repellants, and pheromones. She showed that a single type of chemosensory neuron could express at least four different receptor genes, which could explain the worm's diverse sense of smell (8). Because *C. elegans* has only 14 types of chemosensory neurons but can respond to dozens of different chemicals, each neuronal type was believed to detect multiple stimuli. Bargmann helped confirm this by describing over 40 divergent GPCRs, in gene clusters of two to nine members, that could contribute to such functional diversity.

In genetic screens of olfactory recognition and signal transduction, Bargmann identified *odr-10*, which proved to be a bona fide receptor for a single odorant, diacetyl (9). Mutants of *odr-10* could not detect diacetyl, which is produced by lactobacilli (a food source of *C. elegans*) and is normally attractive to the worm. Upon cloning the *odr-10* gene, Bargmann found that it encoded a novel GPCR. This study was hailed as providing the first direct biological demonstration that a specific GPCR recognized a specific odorant.

One gene that varies among normal individuals accounted for a major behavioral difference.

The defining factor in whether an odorant was attractive or repellent did not lie in the receptor itself, but in the sensory neuron in which it was located. Bargmann and colleagues demonstrated this in a 1997 paper in which they expressed the ODR-10 receptor in neurons that normally detect repellant compounds (10). This misplaced receptor caused the animal to avoid diacetyl, a previously preferred odorant. This result suggested that specific behavioral responses are wired to individual olfactory neurons. "It's not that there isn't learning or experience in behaviors," says Bargmann, "but there is a pre-patterning of appropriate behaviors."

In 2002, Bargmann and colleagues illustrated this prewired behavior by introducing a foreign receptor, the mammalian receptor for capsaicin, into *C. elegans* neurons (11). Because *C. elegans* does not naturally have any ion channels that react with capsaicin, they normally have no reaction when exposed to it. However, placing the mammalian receptor into the nematode's repellant-detecting neurons caused the worm to avoid capsaicin. Therefore, a new artificial behavior was born from stimulating the appropriate neuron.

As Bargmann continued to probe *C. elegans*' olfactory system, her work began uncovering the mechanisms of more complex behaviors. Because each chemosensory neuron could detect a number of different odorants, she believed that *C. elegans* could discriminate between those compounds. Using a forward genetic screen, Bargmann's laboratory identified a mutant able to detect and respond to different odorants but lacking the ability to discriminate between them (12). Studies of the mutant phenotype showed that the worm could discriminate odorants by segregating the detection of different odors into two distinct but similar olfactory neurons. The gene responsible for this mutant phenotype, *nsy-1*, was later found to regulate neuronal asymmetry and diversity.

Although Bargmann and her group generally studied laboratory-induced mutations, they also wanted to increase their understanding of the natural genetic variation in complex behaviors, such as why different populations of *C. elegans* in the wild exhibit either solitary or social feeding behavior. Bargmann showed that such differences in feeding behavior were due to different isoforms of the *npr-1* gene, which encodes a homolog of the neuropeptide Y receptor (13). The social feeding strain carried one isoform, NPR-1 215F, whereas the solitary feeders possessed isoform NPR-1 215V. When NPR-1 215V was expressed in the social feeding strain, the worms' behavior changed to that of solitary diners. This result showed that one gene that varies among normal individuals accounted for a major behavioral difference.

Bargmann later discovered that environmental factors also govern social feeding in *C. elegans*. "We've known that all animals can aggregate under certain conditions, but we didn't know what was acting as a sensory trigger for aggregation," she says. "We've found recently that one of those signals is oxygen." With colleague Michael Marletta of the University of California, Berkeley, Bargmann identified a guanylate cyclase homolog as the molecule responsible for sensing oxygen and generating the behavioral response to undesirable oxygen levels (14). They demonstrated that social feeding requires the activity of this molecule, and such feeding occurs only when oxygen exceeds the nematode's preferred level.

Back to Basics

In addition to elucidating the molecular mechanisms underlying *C. elegans*

nervous system function, Bargmann is also investigating the genesis of the brain. ''We wanted to have a deep understanding of the system we worked in,'' she says. ''That requires understanding the development of these neural circuits.'' In 1998, Bargmann's laboratory identified and cloned the gene *sax-3* (*Robo*), which functions as a receptor in axon guidance (15).

In the laboratory next door, Marc Tessier-Lavigne, currently senior vice president of Research Drug Discovery at Genentech (South San Francisco, CA), was also studying axon guidance, as well as the molecules that guide vertebral axonal growth. Bargmann and Tessier-Lavigne began a long-term collaboration, which continues to produce insight into the molecules that match axons with their appropriate targets (16–18). Bargmann recently demonstrated that neurons establish their connections with the help of other cells and molecules that act as guideposts, such as the synaptic guidepost protein SYG-2 and its receptor SYG-1 (19, 20). SYG-1 acts as a matchmaker by allowing the correct connections to form between neurons.

Bargmann acknowledges the importance of collaborators such as Tessier-Lavigne in her research career. ''At least half my papers have been published together with at least one other group,'' she says. ''It's great because it allows me to engage my dilettantish interest in many things without having to sacrifice high standards.''

Connecting the Dots

From genetics to behavior, Bargmann has identified key pieces of the puzzle of olfactory function in *C. elegans*. In her Inaugural Article (1), Bargmann presents an entire neural circuit for *C. elegans* navigation, which has been done only a few times for simple withdrawal and escape behaviors.

In this PNAS study, Bargmann took advantage of having ''a wiring diagram for the worm brain'' and used that schematic, with laser ablation, ''to trace a path from a sensory input all the way to the different motor outputs that generate behaviors.'' By ablating different sets of neurons one at a time, then removing the nematodes from their food source, Bargmann and colleagues were able to determine which neurons governed each aspect of the worm's sinuous navigational path to find food. ''I've been trying to do this experiment since I was a postdoc,'' she says. Jesse Gray, a graduate student of Bargmann's and the lead author of the article, ''was able to figure it out by conceptualizing the problem in the right way. . . . I feel that he's been able to talk to the neurons in their own language.''

Even with such a seemingly simple system, *C. elegans*' sense of smell contributes to a vast diversity of behaviors. Understanding this system may contribute to understanding more complex mammalian systems and will surely keep Bargmann occupied for many years. ''When you work on *C. elegans*, people are always asking you if you're ever going to work on vertebrates,'' she says. ''But I actually think this is a great system for studying behavior.'' Studying behavior in a vertebrate model such as the mouse is ''just too complicated—they're too smart, they've got too much on their minds,'' says Bargmann. ''A worm, maybe I can figure out.''

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